The hypothalamus-pituitary-adrenal axis in sepsis- and hyperinflammation-induced critical illness: Gaps in current knowledge and future translational research directions

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Summary

The classical model of the vital increase in systemic glucocorticoid availability in response to sepsis- and hyperinflammation-induced critical illness is one of an activated hypothalamus-pituitary-adrenocortical axis. However, research performed in the last decade has challenged this rather simple model and has unveiled a more complex, time-dependent set of responses. ACTH-driven cortisol production is only briefly increased, rapidly followed by orchestrated peripheral adaptations that maintain increased cortisol availability for target tissues without continued need for increased cortisol production and by changes at the target tissues that guide and titrate cortisol action matched to tissue-specific needs. One can speculate that these acute changes are adaptive and that treatment with stress-doses of hydrocortisone may negatively interfere with these adaptive changes. These insights also suggest that prolonged critically ill patients, treated in the ICU for several weeks, may develop central adrenal insufficiency, although it remains unclear how to best diagnose and treat this condition.

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Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated or overactive set of host responses to an infection, which results in critical illness requiring support of vital organ systems in an intensive care unit (ICU).[1] The host responses to sepsis are triggered by recognition of pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs) and, indirectly, by recognition of damage-associated molecular patterns (DAMPs).[2,3] DAMPs are also induced by extensive or complicated surgery and by trauma, triggering hyper-inflammation quite similar as in sepsis.[2,4–6] Hence, we here discuss sepsis-induced as well as hyperinflammation-induced critical illness as one entity.

A vital part of the host response to sepsis- and hyperinflammation-induced critical illness is a swift and robust increase in systemic glucocorticoid availability which is required to prevent imbalanced and excessive immune responses and to bring about essential cardiovascular effects, such as fluid retention and vasoconstriction, and metabolic effects such as activated catabolism and suppressed anabolism for generation of essential metabolic substrates for the "fight or flight" response. Hence, cortisol (in humans) or corticosterone (in mice) is the key "fight or flight" glucocorticoid that mediates protection against sepsis- and hyperinflammation-induced organ failure and death. The classical model of the vital increase in systemic glucocorticoid availability is one of an activated hypothalamus-pituitary-adrenocortical (HPA) axis (Figure 1). It is assumed that sepsis and hyperinflammation, as any other type of stressor, centrally increases the hypothalamic release of corticotropin-releasing hormone (CRH) which, together with vasopressin (AVP), activates the pituitary corticotropes to process and release corticotropin (ACTH) in the circulation which in turn activates the zona fasciculata of the adrenal cortex to synthetize and release cortisol/corticosterone in the circulation.[7] However, studies performed over the last decade have challenged this rather simple model of a central HPA axis activation in critical illness. The results from this work have unveiled a more complex and time-dependent pattern of HPA responses that occur while modern intensive care is applied to circumvent the lethal consequences of sepsis- or other forms of hyperinflammation-induced critical

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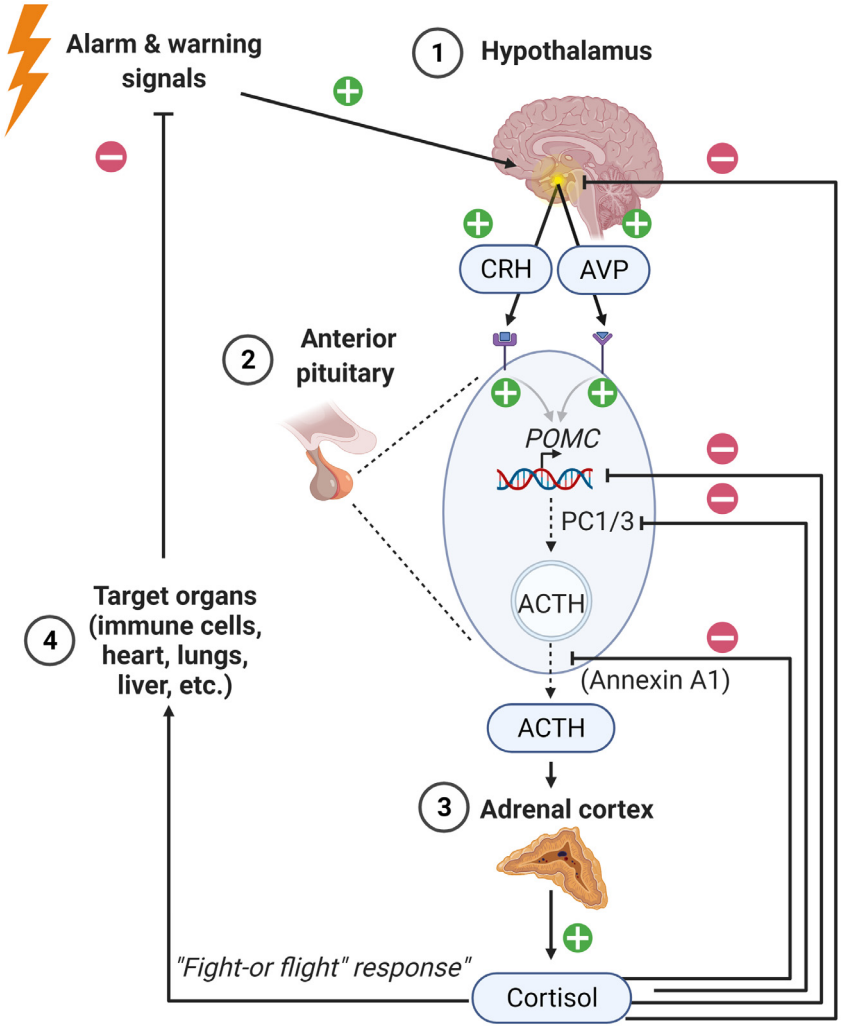

Figure 1. Sepsis and hyperinflammation centrally activate the hypothalamus-pituitary-adrenocortical (HPA) axis.

A variety of sepsis- or hyperinflammation-induced warning and alarm signals are integrated in the hypothalamic paraventricular nucleus, which in response releases CRH and AVP in the hypophyseal portal system. In turn, the corticotropes in the anterior pituitary are activated and start producing the precursor hormone POMC, which is cleaved by PC1/3 into ACTH, and release already produced and stored ACTH into the systemic circulation. ACTH stimulates the adrenal cortex to synthesize and secrete cortisol to initiate the hormonal 'fight-or-flight' response. Cortisol exerts a broad spectrum of effects in a variety of target cells and tissues, in order to cope with and overcome the illness-inducing insults. In addition, cortisol exerts suppressive effects at the hypothalamus and pituitary gland, the latter via suppressing PC1/3 processing of POMC into ACTH and via suppressing ACTH release through upregulation of Annexin A1, collectively designed to shut off the activated HPA-axis.

ACTH: adrenocorticotropic hormone; AVP: vasopressin; CRH: corticotropin-releasing hormone; PC1/3: prohormone convertase 1; POMC: proopiomelanocortin. Created with Biorender.com.

illness. In this review article, these novel insights- with specific focus on regulation and function of the zona fasciculata of the adrenal cortex- and their diagnostic and therapeutic implications are summarized and integrated into a new conceptual framework, followed by the identification of remaining knowledge gaps and by the provision of directions for future translational research.

A decade of translational research generated novel insights in the dynamic HPA axis responses to sepsis and hyperinflammation-induced critical illnesses

A crucial insight that challenged the classical model was the finding that a central HPA axis activation, with elevated ACTH driving increased adrenocortical cortisol production, in response to sepsis or critical illness is very short-lasting (Figure 2).[8] Indeed, studies of human

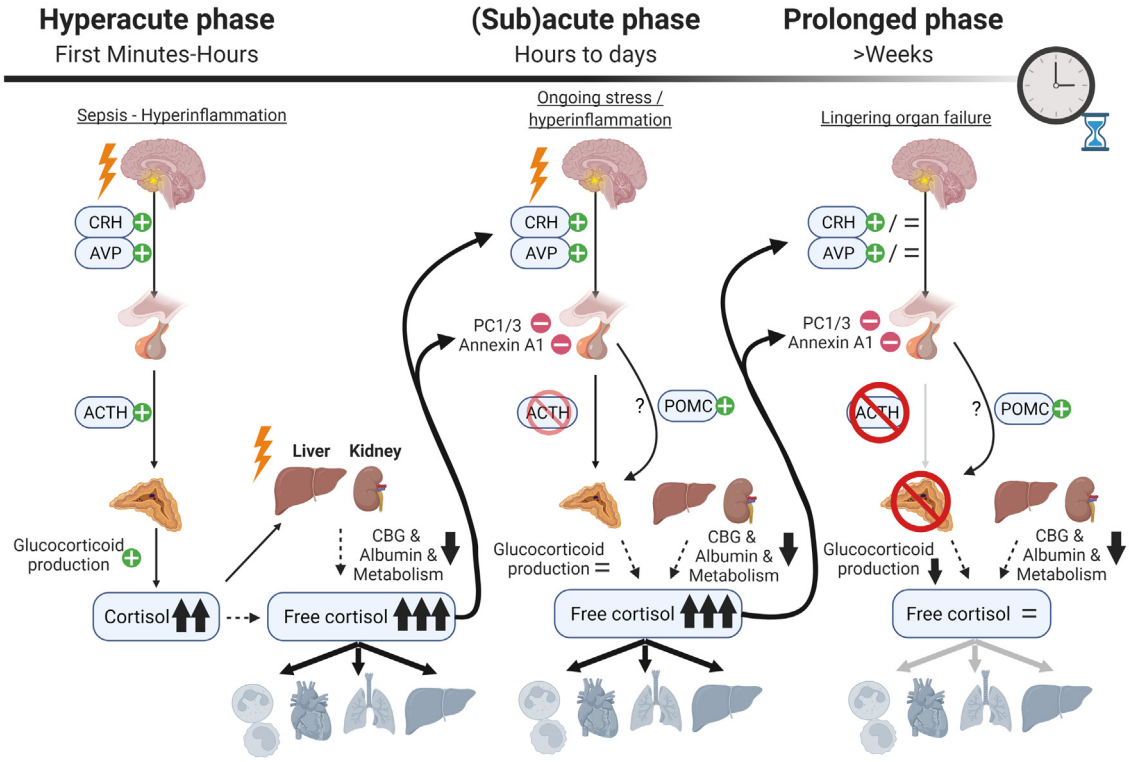

Figure 2. HPA-axis function throughout the various phases of sepsis- and hyperinflammation-induced critical illness.

In this framework, the sepsis and hyperinflammation-induced alterations within the HPA-axis are illustrated, in relation to the duration of illness (phases of critical illness). In the hyperacute phase, minutes to hours after the illness-inducing insult, the HPA-axis is centrally activated, resulting in a rapid and substantial increase in plasma total cortisol. A fast decline in plasma concentrations of cortisol carrier proteins, albumin and CBG, and of cortisol metabolism in liver and kidney, further increase the amount of free cortisol in the circulation. In the (sub)acute phase, the increase in systemic glucocorticoid availability exerts negative feedback at the hypothalamus and at the pituitary, the latter by suppressing PC1/3-mediated processing of POMC into ACTH and by increasing Annexin A1, a potent inhibitor of mature ACTH secretion from the pituitary. Meanwhile ongoing stress continues to stimulate pituitary POMC production via preserved CRH- and AVP-signaling, counteracting the negative feedback exerted by the increased systemic glucocorticoid availability. Plasma free cortisol concentrations remain high via the reduced carrier proteins and suppressed hepatic and renal breakdown and possibly also via (limited) POMC-mediated stimulation of the adrenal cortex. In the prolonged phase, the ongoing low circulating ACTH can result in deprivation of trophic signaling at the adrenal cortex, causing a dysfunction of the adrenal gland. As a results, plasma total and free cortisol start to decline, despite the ongoing severe illness.

ACTH: adrenocorticotropic hormone; AVP: vasopressin; CBG: cortisol-binding globulin; CRH: corticotropin-releasing hormone; PC1/3: prohormone convertase 1; POMC: proopiomelanocortin. Created with Biorender.com.

patients suffering from sepsis- or hyperinflammation-induced critical illness and treated in the intensive care unit have failed to show an increase in ACTH plasma concentration from ICU admission onwards.[2,9] In fact, an increased plasma ACTH, quantified by the more recent assays that, unlike older assays, are highly specific for ACTH,[10,11] has only been documented to be present transiently, such as during surgery, whereas thereafter, and at least throughout the first week in the ICU, plasma ACTH is always lower than normal whereas plasma cortisol is elevated.[9,12] Studies of critically ill patients, that have used state of the art tracer technology or deconvolution analysis of hormonal time series, have reported cortisol production rates that are only slightly higher than normal during the day and ACTH-driven pulsatile cortisol secretion rates that are lower than normal during the night.[9,13] Hence, except for a swift though transient central HPA axis activation, such an activation is not present in ICU patients and yet, systemic cortisol availability is and remains clearly increased. This constellation was also present in a clinically relevant, fluid-resuscitated and intensive care supported mouse model of sepsis-induced critical illness, with plasma corticosterone levels that are high in the absence of increased ACTH.[14,15]

After the initial very short-lasting central HPA axis activation, a series of orchestrated peripheral adaptations rapidly set in to maintain increased cortisol availability for target tissues without a continued need for increased cortisol production (Figure 3).

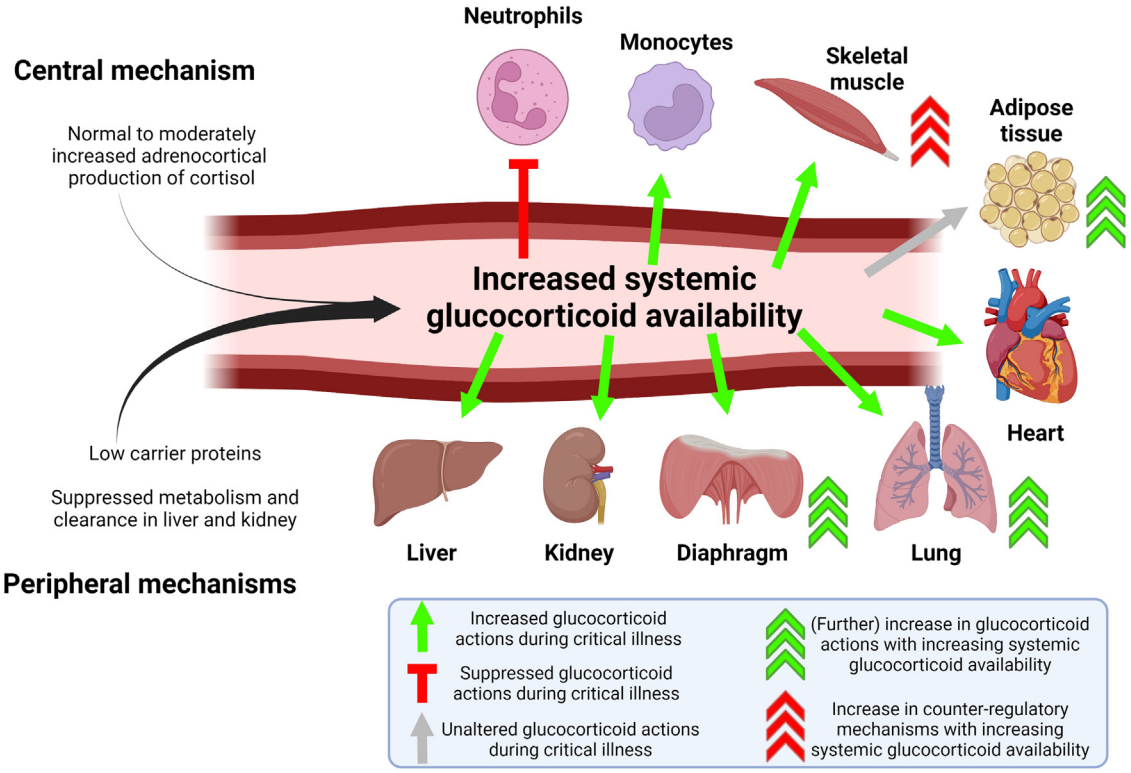

Figure 3. Maintenance and guidance of the increased systemic glucocorticoid availability.

A series of orchestrated peripheral adaptations maintain increased systemic cortisol availability for target tissues without (a continued need for) increased cortisol production. The actions of the increased circulating cortisol are selectively guided towards those tissue that may benefit from the immune or catabolic, fight-or-flight effects, while other tissues that may be harmed are, at least partially, protected. Created with Biorender.com.

A first highly effective peripheral adaptation is the liberation of circulating cortisol from the plasma binding proteins, transcortin (CBG) and albumin, so that the free and active form of cortisol increases.[16,17] This is brought about by a reduction in hepatic synthesis of these binding proteins and by an altered binding affinity of cortisol for its binding proteins.[15–18] As a result, the distribution volume of cortisol increases rapidly and cortisol can easily access the target tissues to exert its vital effects.[2,9]

A second peripheral adaptation is the suppression of cortisol breakdown in liver and kidney, which results in an increased cortisol half-life and a further maintenance of a high amount of free cortisol in the circulation and in target tissues. As a result of the high free cortisol in the circulation, negative feedback inhibition is exerted at the hypothalamus and pituitary level of the HPA axis, via central glucocorticoid receptor alfa (GRα)-ligand binding. While expression of hypothalamic CRH and AVP was shown to be increased early in sepsis, this became normalized thereafter which could be the net balance of continued central activation and concomitant suppression via feedback-inhibition.[14,19] At the pituitary level, the expression of the enzyme prohormone convertase 1 (PC1/3), the enzyme that is responsible for the conversion of the prohormone of ACTH, proopiomelanocortin (POMC) into ACTH, was shown to be suppressed in a mouse model of sepsis, the expected result of pituitary GRα-ligand binding. Sepsis was also shown to increase the pituitary expression of Annexin A1 in the mouse model. Annexin A1 is a known mediator of the feedback actions of glucocorticoids at the pituitary level via its suppressive effect on the secretion of ACTH from the anterior pituitary into the circulation. As a result, in sepsis, the expression of the prohormone POMC at the pituitary level continues while it is not processed into ACTH leading to reduced levels of circulating ACTH and accumulation of POMC that subsequently leaks into the circulation through the constitutive pathway. Indeed, studies have now reported a robust and continued rise in plasma POMC concentrations throughout acute and prolonged human critical illness.[14] In another mouse study of adrenal explants, POMC has shown to increase steroidogenesis in the zona fasciculata of the adrenal cortex in the absence of ACTH.[19] Hence, in sepsis, the low levels of circulating ACTH may explain progressive loss of adrenocortical structure and integrity, as documented in a septic

mouse model and in prolonged critically ill patients, while some degree of ongoing steroidogenesis may be brought about in part by the increased amount of circulating POMC.[14,19,20]

A third set of acute peripheral adaptations occur at the level of the various glucocorticoid target tissues, which guide and titrate cortisol action to match their individual needs. Outside the context of intensive care, it is well known that cortisol or synthetic glucocorticoids exert quite different effects depending on the type of target tissue. Until recently, such tissue-specific regulation of cortisol action was not taken into account in the context of critical illness. Some clinical studies of sepsis had reported reduced gene expression of the active glucocorticoid receptor (GRα) in peripheral blood.[21–24] This was then interpreted as a marker of "generalized resistance" to glucocorticoids and was considered to be an argument for treating patients with sepsis or septic shock with high doses of hydrocortisone to "overcome the resistance". However, blood is composed of a mixture of cell types that may respond differently, and, also, it remained unclear whether other cortisol target tissues show similar GRα suppression. Likewise, studies of murine sepsis, which selectively manipulated hepatic GRα signaling to evoke glucocorticoid resistance in the liver, may have over-interpreted their results as being reflective of what happens in other target tissues.[25,26] Evidently, the GRα in the liver and its downstream signaling are essential for survival, in part due to the key metabolic effects in the liver that are brought about by cortisol.[15,25] This was corroborated by an increased risk of death evoked by inducing defective hepatic GRα signaling in a mouse model.[25] In another study, it was shown that a partial reduction in the expression of GRα, through small hairpin RNA, selectively in the liver leads to local and systemic hyperinflammation and to worsening of the outcome of sepsis.[15] These findings confirmed a key role for a functional GRα in the liver in the struggle for survival from sepsis. However, an adaptive downregulation of the hepatic GRα in sepsis may occur in response to the initial GRα ligand binding by cortisol, and this may be beneficial rather than deleterious, for example through bringing about an acute lowering of CBG as a fast feed-forward loop to rapidly increase systemic cortisol availability.[15] Also, as is the case for the studies reporting downregulation of the GRα in the blood, the results of studies investigating experimental alterations selectively to the hepatic GRα cannot be extrapolated to other organs and tissues. A recent set of studies, performed in human critically ill patients with sepsis and in a clinically relevant mouse model of sepsis-induced critical illness have revealed that a "generalized resistance" to glucocorticoids is in fact not present.[5] In contrast, these studies have shown that in sepsis, certain cells and tissues downregulate GRα action whereas others upregulate GRα action. Most strikingly, it was shown that in neutrophils gene expression of the GRα as well as GRα action, reflected by suppressed expression of glucocorticoid-induced leucine zipper (GILZ), were suppressed throughout critical illness. This could point to an adaptive response which safeguards the activated innate immune response of neutrophils to critical illness. There was no difference in GRα or GILZ expression between critically ill patients with or without sepsis upon admission. In contrast, increased GRα action was present in monocytes - shown to be an essential response for effective bacterial killing[27] - as well as in all other (vital) target tissues not in the least the lungs.[5] It was also shown that local GRα action was not only determined by the level of receptor expression but also by the degree of local cortisol production via 11β-hydroxysteroid dehydrogenase 1 (11bHSD1) and by the expression of the GRα-ligand binding induced FK506 binding protein 5 (FKBP51), an inhibitor of GRα sensitivity. These recent studies also showed that further increasing glucocorticoid availability, such as by infusion of high doses of hydrocortisone, (a) did not overcome the glucocorticoid resistance in neutrophils (GRα expression and action was substantially suppressed and stayed suppressed upon treatment), (b) triggered adaptive responses to prevent a rise in GRα action in other tissues such as skeletal muscle and (c) only in the lung and the diaphragm resulted in a further rise of GRα action. Such an array of tissue-specific alterations in the action of the GRα appears to a large extent adaptive and beneficial for the host. Increased GRα action in the lungs and the further increase in such action in response to treatment with high dose glucocorticoids may also offer some explanation for the inconsistent outcomes of RCTs that have investigated the impact of pharmacological doses of glucocorticoids in sepsis. In particular, selected studies of sepsis of pulmonary origin, such as evoked by COVID-19 or by community acquired pneumonia, or studies of non-COVID acute respiratory distress syndrome have shown beneficial outcome effects of glucocorticoids,[28–30] whereas other studies of more heterogeneous patient populations did not consistently find such benefit.[31–34] However, a sub-analysis of the ADRENAL trial did not show a mortality benefit in the subgroup of patients who suffered from sepsis from pulmonary origin.[33] On the other hand, the response to glucocorticoid treatment in sepsis and septic shock may also depend on the transcriptomic profile, referred to as sepsis response signatures or SRS, of the target cells and tissues.[35,36] However, transcriptomic SRS have only been defined with use of mRNA extracted from peripheral blood. It is again possible that other glucocorticoid target tissues behave differently, a possibility that has not yet been investigated.

Also, the adaptive downregulation of GRα action in tissues that are vulnerable for side effects of high glucocorticoid availability, as was shown for neutrophils and in part also skeletal muscle, may be interpreted as

beneficial. However, unlike skeletal muscle, the diaphragm of septic mice did not show these adaptive responses and thus this vital organ may be quite vulnerable for glucocorticoid-induced side effects, such as atrophy, that can lead to respiratory muscle weakness.[37,38]

Prolonged critical illness, a subgroup of patients for whom "adaptations" may turn into "risks"

Whereas the series of orchestrated acute peripheral adaptations to sepsis resulting in maintained increased cortisol availability for target tissues without (a continued need for) increased ACTH-driven cortisol production are likely adaptive and beneficial for the host, it remained unclear whether these responses change when critical illness extends to several weeks and whether they normalize after ICU discharge. In 2018, a clinical study of long-stay ICU patients was published which specifically addressed these questions.[2] Long-stay patients in the ICU beyond 4 weeks, suffering from sepsis and other types of critical illness alike, were found to no longer have elevated plasma total and free cortisol, whereas only upon recovery one week later on a regular ward, both ACTH and cortisol rose above normal.[2] Another study showed that incremental ACTH-responses to a CRH-stimulation test were robustly suppressed in such long-stay ICU patients, indicative of a central HPA axis suppression.[4] Hence, in prolonged critically ill patients in the ICU for several weeks or longer, a central (secondary) adrenal insufficiency may develop. This could the consequence of increased central GRα-ligand binding sustained for several weeks by the peripherally increased cortisol and/or by other GRα-ligands such as bile acids that typically are increased in long-stay ICU patients.[39] This was further supported by a human postmortem study that showed adrenocortical lipid depletion and atrophy and suppressed expression of ACTH-stimulated steroidogenic genes in patients who died after prolonged, but not after brief critical illness.[20] Such central (secondary) adrenal insufficiency may result clinically in lingering otherwise unexplained vasopressor dependency and associated organ failure, encephalopathy, delirium and fatigue, together hampering or delaying recovery. In addition, drugs that are commonly used in the ICU such as opioids and antifungals may further increase this risk of adrenal insufficiency.[40] Also, as shown in a murine sepsis study, treatment with exogenous glucocorticoids in so-called "stress-doses" further increases the risk of central (secondary) adrenal insufficiency and substantially aggravates local inflammation within the adrenal cortex.[19] It remained unclear to what extent and within which time frame ACTH and cortisol normalize after prolonged critical illness. In this regard, a recent study found normalized ACTH and cortisol concentrations 5 years after critical illness.[41] However, this study included both short- and long-stay critically ill patients and may be confounded by survivor bias.

Diagnostic and therapeutic implications of the evolving evidence

These insights in the HPA axis to sepsis- and hyperinflammation-induced critical illness responses (summarized in Table 1) already have a few diagnostic and therapeutic implications.

First, the finding that the distribution volume for cortisol is robustly increased, in proportion to the degree of suppression of cortisol plasma binding proteins and thus in proportion to the severity of illness and the risk of death, has one major implication. It invalidates the use of the classical ACTH stimulation test (250 µg of synthetic ACTH administered as an IV bolus with documentation of the incremental response in total plasma cortisol) as a diagnostic test to assess the adrenocortical integrity and function in patients with sepsis, septic shock or other types of critical illness.[42,43] Indeed, with such an increase in cortisol distribution volume, the incremental response in total plasma cortisol is always reduced, whereas the incremental response in free plasma cortisol is normal.[2] The sicker the patients, the lower the plasma CBG and the higher the distribution volume and thus the more suppressed the incremental response of total plasma cortisol to the ACTH injection.[2,44] This is in line with an earlier study of patients with septic shock that reported a low increment in total plasma cortisol in response to ACTH injection to be highly predictive of mortality, irrespective of the baseline level of plasma cortisol.[45] Such an association between a low cortisol response to the ACTH stimulation test merely reflects the predictive value of high severity of illness (low CBG and high cortisol distribution volume) rather than being a marker of adrenal insufficiency.[44] The ACTH stimulation test thus cannot be used to identify patients who should be treated with exogenous glucocorticoids, as demonstrated by subsequent randomized controlled trials.[32,34,46] Unfortunately, random total cortisol concentrations also do not provide useful information for clinicians to identify patients who might benefit from increasing systemic glucocorticoid availability with exogenous glucocorticoid treatment, as these levels highly vary between patients and even in a single patient depending on the time of sampling.[43] Similarly, plasma free cortisol concentrations are currently not useful in daily clinical practice as quantification is a complex, expensive and time-consuming process. In addition, there are no validated threshold levels to define what should be considered "too low" or "normal".

Second, these insights may have implications for the treatment of patients with septic shock. Patients with septic shock are severely ill and often require high doses of vasopressors. Vasopressors can often be stopped

Level/aspect of the HPA-axis	Prior theory/assumptions	Insights generated over the past decade	References
Cortisol production	Sustained increased ACTH-driven adrenocortical production and secretion of cortisol: the equivalent of ±200 mg hydrocortisone/24h to reach high plasma cortisol concentrations.	Cortisol production is only moderately or not increased during critical illness: on average the equivalent of ±60 mg of hydrocortisone/24h.	9,13
Increased systemic cortisol availability	Driven by ±10 fold increase in adrenocortical production and secretion of cortisol and by reduced plasma concentrations and binding-affinity of cortisol carrier proteins.	Largely brought about by suppressed cortisol breakdown in liver and kidney and by reduced plasma concentrations and binding-affinity of cortisol carrier proteins, not by increased ACTH-driven cortisol production and secretion.	2,9,15–18
Plasma ACTH concentrations	Ongoing central activation of the HPA-axis results in sustained elevated plasma ACTH concentrations.	Plasma ACTH is only briefly elevated and subsequently suppressed due to negative feedback-inhibition (pituitary GRα ligand binding) impairing pituitary processing of POMC into ACTH and suppressing ACTH secretion.	14,19
GRα expression in cortisol target organs	Suppressed GRα expression in peripheral blood cells of patients admitted to ICU for sepsis, considered to reflect systemic glucocorticoid resistance necessitating treatment with high doses of glucocorticoids.	Tissue-specific alterations in GRα expression and signaling result in suppressed GRα action in neutrophils but increased GRα action in most other organs and tissues. GRα action responses to further increasing systemic glucocorticoid availability are also tissue-specific.	5,15,21–25
Suppressed HPA-axis in prolonged critically ill patients	No data / not considered	Decrease of plasma total and free cortisol concentrations in prolonged critical illness + delayed suppressed ACTH response to CRH test are indicative of central adrenal insufficiency that may develop over weeks in the ICU. Further substantiated by adrenocortical lipid depletion and atrophy of adrenal glands in ICU patients who died after a prolonged, but not brief, critical illness and by rebound HPA-axis activation in the post-ICU recovery phase in survivors.	2,4,20

***Table 1*: Evolving evidence over the past decade in the HPA-axis response to sepsis- and hyperinflammation-induced critical illness.**
ACTH: adrenocorticotropic hormone; GRα: glucocorticoid receptor alpha; HPA: hypothalamic-pituitary-adrenocortical; ICU: intensive care unit; POMC: proopiomelanocortin.

earlier when high stress-doses of hydrocortisone are administered to patients with septic shock.[32–34,47] However, this hemodynamic response to the treatment should be interpreted as a pharmacological effect and not as evidence for insufficient endogenous cortisol availability nor as evidence for "generalized cortisol resistance" that can be overcome by such high stress-doses of hydrocortisone. It should also be taken into account that, although such high doses of glucocorticoids may expectedly reduce lung inflammation, they may also have adverse effects on respiratory muscles and the adrenal cortex among others.[5]

Third, the daily doses of hydrocortisone (200-300 mg) that are currently advised for treatment of septic shock[48] or for other indications in the ICU are the equivalent of at least 10-times the substitution dose of cortisol for otherwise healthy subjects and around 4-fold higher than the average daily cortisol production in critically ill patients.[9] It may not be necessary to use such high doses given the suppressed breakdown of cortisol and the suppressed cortisol plasma binding in critically ill patients. Indeed, it has been shown that administration of stress doses of hydrocortisone results in 9-fold higher plasma free cortisol concentrations as compared with critically ill patients who do not receive glucocorticoid treatment.[49]

Fourth, when a central form of adrenal insufficiency is suspected in patients who are critically ill for several weeks and who show symptoms and signs of adrenal insufficiency, it may be appropriate to treat with hydrocortisone. As a daily dose of 60 mg of hydrocortisone, administered IV as 40 mg in the morning and 20 mg in the evening to mimic some degree of diurnal rhythm, equals the daily production of cortisol that has been documented by tracer technology in the context of critical illness, it is reasonable to consider treatment with

such a more moderate dose.[9,13] However, the patient selection (indication), optimal dose and treatment regime, should all be further investigated in adequately powered RCTs before any firm recommendation can be provided.

Conclusions

The insights in the responses within the HPA axis -with focus on the regulation and function of the zona fasciculata of the adrenal cortex - to sepsis and hyperinflammation-induced critical illness that were gathered over the last decade can be interpreted as revealing an orchestrated and dynamic set of endogenous adaptations that are likely beneficial for the host. Stress doses of hydrocortisone in acute septic shock are a pharmacological intervention that accelerates shock reversal but may also negatively interfere with the adaptive HPA axis changes. The very long-stay ICU patient may develop a central form of adrenal insufficiency after several weeks of critical illness, though it remains to be investigated how to best diagnose and treat this condition.

Outstanding questions

It should be evident from the above that there are still many gaps in the current knowledge and thus many outstanding questions that require further investigation. We list some of them here in random order, to give direction to future translational research.

Although it is now known that there is no "generalized glucocorticoid resistance" in sepsis and hyperinflammation-induced critical illness and that, instead, adaptive, tissue-specific titration of GRα-action is brought about, this conclusion was largely based on the expression of the GRα, of the target gene encoding the chaperone protein FKBP51 and of a very important downstream target gene encoding GILZ. This work is but a first step in the unraveling of the tissue-specific differences in the functional impact of increased cortisol availability in sepsis on immunity and inflammation, on metabolism and organ system functions. This requires experiments in clinically relevant animal models with tissue-specific modulation of the various aspects of the GRα signaling cascade.

The finding that circulating POMC levels are elevated uniformly in human patients and in clinically relevant mouse models of sepsis-induced critical illness, its exact role in maintaining steroidogenesis and its impact on adrenal cortex integrity *in vivo* remains unclear. The available data may suggest that both POMC and ACTH may exert distinct and unique effects on the adrenal cortex. Further investigation would require *in vivo* experiments in clinically relevant models of sepsis with independent manipulation of POMC and ACTH. In addition, any possible role of the many other POMC fragments in the production of steroids within the adrenal gland, remains to be investigated in the context of sepsis.[50] Also, further research should address regulation and function of mineralocorticoids, and their interaction with glucocorticoids, to further unravel the pathophysiology of the stress response to critical illness.

As mentioned, Annexin A1 is a known mediator of the feedback actions of glucocorticoids at the pituitary level, suppressing the secretion of ACTH from the anterior pituitary. However, Annexin A1 may also play a role within the adrenal cortex and in the other neuro-endocrine axes.[51,52] Whether or not a stress- or inflammation-induced upregulation of Annexin A1 plays a role in the pathophysiology within these neuro-endocrine systems in response to critical illness remains to be explored.

More clinically oriented remaining questions comprise the identification of accurate diagnostic criteria for central (secondary) adrenal insufficiency in long-stay ICU patients and to study the impact of treatment on clinically relevant, patient-centered outcomes via adequately powered RCTs. The goal of future research should also be to identify the lowest effective hydrocortisone dose and the shortest effective treatment duration as well as optimal modalities for tapering schedules. In the context of septic shock or pulmonary inflammation, more research should focus on indications for synthetic glucocorticoids versus hydrocortisone (cortisol) which may vary depending on timing and clinical phenotype. Besides treatment with glucocorticoids, the impact of CRH and/or ACTH treatment, or of small molecules developed to specifically modulate their G-protein coupled receptors, as alternative strategies should be investigated. When RCTs are designed to assess the clinical outcomes of the various treatment modalities and/or doses, also a detailed investigation of potential short- and long-term side effects should be added. These include delirium, epigenetic changes, impact on muscle function, neurocognitive decline and emotional problems, and the impact on cardiovascular and bone health to name but a few.

Search strategy and selection criteria

(Sepsis OR critical-illness) AND (cortisol OR HPA)

This is a narrative review of the Pubmed-searched literature available predominantly from the last decade from which we selected the studies, performed in *in vivo*, clinically relevant animal models and in human patients, that provided insights in the pathophysiology of the HPA axis function and/or cortisol action in sepsis or critical illness.

Contributors

Writing - original draft: Greet Van den Berghe; writing - review & editing: Lies Langouche, Arno Téblick, Jan Gunst. All authors read and approved the final version of the manuscript.

Data sharing statement

Not applicable: review article.

Declaration of interests

We declare no competing interests.

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